An Appendix including amended drawing figures is attached following page 16 of this paper

Amendment to the Specification:

Please replace paragraphs [0013], [0014], [0015], [0023] and [0038], as published, with the following amended paragraphs:

[0013] FIG. 2A is a histogram of the particle diameter of batch 1 of the microspheres before sterilization~~, sterilized at room temperature,~~ and sterilized at <5 °C (Cold Pack)~~, and an overlay of the batch sterilized at <5 °C and the batch before sterilization~~. FIG. 2B is a histogram of the particle diameter of batch 1 of the microspheres sterilized at room temperature and an overlay of the batch sterilized at ≤5 °C and the batch before sterilization.

[0014] FIG. 3A is a histogram of the particle diameter of batch 2 of the microspheres before sterilization~~, sterilized at room temperature,~~ and sterilized at <5 °C (Cold Pack)~~, and an overlay of the batch sterilized at <5 °C. and the batch before sterilization~~. FIG. 3B is a histogram of the particle diameter of batch 2 of the microspheres sterilized at room temperature and an overlay of the batch sterilized at ≤5 °C and the batch before sterilization.

[0015] FIG. 4A is a histogram of the particle diameter of batch 3 of the microspheres before sterilization~~, sterilized at room temperature,~~ and sterilized at <5 °C (Cold Pack)~~, and an overlay of the batch sterilized at <5 °C and the batch before sterilization~~. FIG. 4B is a histogram of the particle diameter of batch 3 of the microspheres sterilized at room temperature and an overlay of the batch sterilized at ≤5 °C and the batch before sterilization.

[0023] The term irradiation refers to the process of exposing the sample to a form of radiation. The type and dose of the radiation used in the irradiation process can be

determined by one of ordinary skill in the art by considering the type of polymeric material, the type of any therapeutically active agent that may be present, and the use for which the polymeric material is intended. While not intending to limit the scope of invention, in many cases the dose of the radiation would be similar to that used when sterilizing the sample without external cooling. If the cooling apparatus is comprised of a material that would scatter, reflect, absorb, or otherwise decrease the dose of the radiation received by the sample, the dose should be increased accordingly. While not intending to limit the scope of the invention, some examples of radiation useful in this invention include gamma radiation, alpha radiation, beta radiation, microwave radiation, and ultraviolet radiation. In the preferred embodiment of this invention the polymeric material is sterilized by gamma irradiation. In a more preferred embodiment of this invention, the sterilization is by gamma irradiation at a dose of about 1.5 to about 4.0 ~~mRad~~ Mrad.

[0038] The freeze-dried microspheres were then sterilized. Each of the two batches were divided into three groups, as depicted in Table 1. The first group, the control group, was not sterilized; the second group was packaged and sterilized at <5°C by gamma irradiation at a dose of 2.5 to 4.0 ~~mRad~~ Mrad; and the third group was packaged and sterilized at 25°C by gamma irradiation at a dose of 2.5 to 4.0 ~~mRad~~ Mrad. Cooling during the <5°C sterilization was accomplished by the use of Cold Packs coupled and specialized packaging [product available as WMX, from DHL, Paris France]. Temperature was monitored by a 3M MonitorMark Temperature Indicator, St. Paul, MN, ensuring the temperature did not exceed 5°C. Turning to Figure 1 significant aggregation was observed by microscopy in both drug loaded and unloaded (no pharmaceutically active agent) microspheres which were sterilized by gamma irradiation at 25°C. By contrast, ~~the~~ both the drug loaded and unloaded microspheres which were sterilized at <5°C have significantly less aggregation. Figures 2-4 detail the particle diameter distribution of the various batches before and after gamma irradiation. A significant increase in average particle diameter and in the breadth fo the distribution particle diameters is observed for all batches of microspheres which were sterilized at 25°C. By contrast those batches of microspheres which were sterilized at a reduced

temperature show an essentially identical volume and number average particle size distribution with their non-sterilized counterparts. There results demonstrate that the aggregation of PLGA microspheres due to gamma irradiation is essentially eliminated by reducing the temperature of the microspheres to around 5°C or less during the sterilization.